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(54) Title: USE OF GABAPENTIN IN THE TREATMENT OF ANXIETY AND PANIC

(57) Abstract

The instant invention is novel uses of known cyclic amino acids. Such compounds as gabapentin are useful in the treatment of anxiety and in the treatment and/or prevention of panic attacks. The partial N-terminal sequence of the gabapentin binding protein has been determined to be identical to the N-terminal sequence of the mature $\alpha_2\delta$ subunit of the L-type Ca^{2+} channel from rabbit skeletal muscle.

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USE OF GABAPENTIN IN THE TREATMENT OF ANXIETY AND PANIC

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BACKGROUND OF THE INVENTION

The present invention relates to novel therapeutic uses of a known compound, gabapentin, its derivatives, and pharmaceutically acceptable salts. The present invention concerns a method for treating and/or preventing anxiety in a mammal in need of such treatment. It also concerns treating and/or preventing panic attacks in a mammal.

United States Patent 5,084,479 concerns a method for treating neurodegenerative disorders.

Such neurodegenerative disorders are, for example, Alzheimer's disease, Huntingdon's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. It also covers treating those neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

Stroke refers to a cerebral vascular disease or a cerebral vascular incident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia. It is also useful in a patient undergoing specifically carotid endart rectomy or in general other cerebrovascular or

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vascular surgical procedures or diagnostic vascular procedures including cerebral angiography and the like.

5 Other incidents are spinal cord trauma or injury from general anoxia, hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

United States Patent 4,024,175 and its divisional 4,087,544 cover the compounds of the instant invention, methods for preparing them, and several uses thereof.

10 The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The

15 compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

There is no disclosure in the above references to make obvious the present invention of novel uses of compounds of United States Patent 4,024,175 to treat

20 anxiety.

Gabapentin (Neurontin®) is a structural analogue of γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in mammalian brain. However, unlike GABA, it readily penetrates the blood-brain barrier and

25 it does not interact with either GABA_A or GABA_B receptors (Bartoszyk D.G. and Reimann W. (1985), Preclinical characterization of the anticonvulsant gabapentin. In: 16th Epilepsy International Congress. Abstracts (Ciba-Geigy, Basel), Page 1). It has been

30 shown to possess anticonvulsant activity in a wide range of animal seizure models. The spectrum of anticonvulsant activity for gabapentin predicted from these preclinical studies includes partial seizures and generalized tonic-clonic seizures. This has been

35 confirmed in clinical studies (Goe K.L., Sorkin E.M. Gabapentin: A review of its pharmacological properties

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and clinical potential in epilepsy. Drug Evaluation,
46(3):409-427 (1993)). Patent Application WO 93/23383
covers gamma aminobutyric acid (GABA) and L-glutamic
acid analogs for seizure treatment. It also discloses
a treatment of depression, anxiety, and psychosis.

SUMMARY OF THE INVENTION

Gabapentin is currently under clinical use as an
adjunctive treatment of partial seizures and partial
seizures with secondary generalization in patients not
satisfactorily controlled by or intolerant to
conventional therapies. The mode of action of
gabapentin was previously unknown but was thought to
involve a novel, yet undefined, mechanism of
antiepileptic action involving affinity for a
previously unidentified binding site in the brain
(Hill D.R., et al., Localization of [³H]gabapentin to a
novel site in rat brain: autoradiographic studies.
Eur. J. Pharmacol.-Mol. Pharmacol. Sec., 244:303-309
(1993) and [³H]-Gabapentin binds to a novel site in rat
cortical synaptic plasma membranes (Suman-Chauhan N.,
et al., British Journal of Pharmacology Proceedings
Supplement, 71P:July 10-12, 1991)

We have now purified the gabapentin binding
protein and determined the sequence of the first ten
amino acid residues (EPFPSAVTIK). From this result we
deduce that the gabapentin binding protein is an $\alpha_2\delta$
subunit of a brain calcium channel. Further compounds
interacting with the $\alpha_2\delta$ subunit of the Ca²⁺ channel
will have anxiolytic, antipanic, and anticonvulsant
activity. We have now discovered that gabapentin,
isobutylGABA, and similar compounds bind to the
[³H] gabapentin binding protein in rat, pig, and human
brain.

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In the present study we have examined gabapentin in four animal models.

The instant invention is a new use of the known compound gabapentin (Neurontin®); chemical name
5 1-(aminomethyl)cyclohexaneacetic acid. The compound is useful as an anxiolytic and as an agent in treating and/or preventing panic attacks.

10

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of gabapentin in the mouse light/dark box.

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Figure 2 shows the effect of gabapentin in the rat elevated X-maze.

Figure 3 shows the effect of gabapentin in the human marmoset threat test.

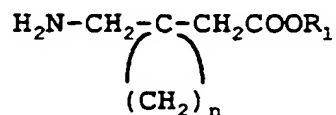
Figure 4 shows the effect of gabapentin and CDP in the rat conflict test.

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DETAILED DESCRIPTION

25 The present invention relates to novel methods of treating anxiolytic diseases or panic in a mammal in need of such treatment. The treatment comprises administering in unit dosage form a therapeutically effective amount of a compound of formula

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wherein R_1 is hydrogen or a lower alkyl and n is 4, 5, or 6 or a pharmaceutically acceptable salt thereof.

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The term lower alkyl includes straight or branched chain alkyl groups of up to 8 carbon atoms.

Preferred compounds of Formula I above include but are not limited to 1-aminomethyl-1-cyclohexane-acetic acid, ethyl 1-aminomethyl-1-cyclohexane-acetate, 1-aminomethyl-1-cycloheptane-acetic acid, 1-aminomethyl-1-cyclopentane-acetic acid, methyl 1-aminomethyl-1-cyclohexane-acetate, n-butyl 1-aminomethyl-1-cyclohexane-acetate, methyl 1-aminomethyl-1-cycloheptane-acetate, n-butyl 1-aminomethyl-1-cycloheptane-acetate, toluene sulfonate, 1-aminomethyl-1-cyclopentane-acetate, benzene-sulfonate, and n-butyl 1-aminomethyl-1-cyclopentane-acetate.

The most preferred compound is 1-aminomethyl-cyclohexane acetic acid (gabapentin).

Pharmaceutical compositions of the compound of the present invention or its salts are produced by formulating the active compound in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol; glycerin; sorbitol; polyethylene glycol; water; agar; alginic

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acid; isotonic saline; and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

The percentage of the active ingredient in the foregoing compositions can be varied within wide limits but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present.

Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 50 to 600 mg, preferably between 20 and 200 mg.

A unit dosage form of the instant invention may also comprise other compounds useful in the therapy of anxiety and diseases involving anxiety.

The advantages of using the compounds of Formula I, especially gabapentin, in the instant invention include the relatively nontoxic nature of the compound, the ease of preparation, the fact that the compound is well tolerated, and the ease of IV administration of the drug. Furthermore, the drug is not metabolized in the body.

The subjects used herein are mammals, including humans.

The usefulness of compounds of Formula I above and the salts thereof as agents for anxiety and for panic

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is demonstrated in standard pharmacological test procedures.

5

MATERIAL AND METHODS

Animals

Male Hooded Lister rats (200-250 g) were obtained from Interfauna (Huntingdon, UK) and male TO mice (20-25 g) were obtained from Bantin and Kingman (Hull, UK). Both rodent species were housed in groups of six. Ten Common Marmosets (*Callithrix Jacchus*) weighing between 280 and 360 g, bred at Manchester University Medical School (Manchester, UK) were housed in pairs. All animals were housed under a 12-hour light/dark cycle (lights on at 07.00 hour) and with food and water ad libitum.

Drug Administration

Drugs were administered either intraperitoneally (IP) or subcutaneously (SC) 40 minutes before the test in a volume of 1 mL/kg for rats and marmosets and 10 mL/kg for mice.

Mouse Light/Dark Box

The apparatus was an open-topped box, 45 cm long, 27 cm wide, and 27 cm high, divided into a small (2/5) and a large (3/5) area by a partition that extended 20 cm above the walls (Costall B., et al., Exploration of mice in a black and white box: validation as a model of anxiety. Pharmacol. Biochem. Behav., 32:777-785 (1989)).

There was a 7.5 x 7.5 cm opening in the center of the partition at floor level. The small compartment was painted black and the large compartment white. The white compartment was illuminated by a 60-W tungsten

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bulb. The laboratory was illuminated by red light. Each mouse was tested by placing it in the center of the white area and allowing it to explore the novel environment for 5 minutes. The time spent in the illuminated side was measured (Kilfoil T., et al., Effects of anxiolytic and anxiogenic drugs on exploratory activity in a simple model of anxiety in mice. Neuropharmacol., 28:901-905 (1989)).

10 Rat Elevated X-Maze

A standard elevated X-maze (Handley S.L., et al., Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behavior. Naunyn-Schiedeberg's Arch. Pharmacol., 327:1-5 (1984)), was automated as previously described (Field, et al., Automation of the rat elevated X-maze test of anxiety. Br. J. Pharmacol., 102(Suppl):304P (1991)). The animals were placed on the center of the X-maze facing one of the open arms. For determining anxiolytic effects the entries and time spent on the end half sections of the open arms was measured during the 5-minute test period (Costall, et al., Use of the elevated plus maze to assess anxiolytic potential in the rat. Br. J. Pharmacol., 96(Suppl):312P (1989)).

25 Marmoset Human Threat Test

The total number of body postures exhibited by the animal towards the threat stimulus (a human standing approximately 0.5 m away from the marmoset cage and staring into the eyes of the marmoset) was recorded during the 2-minute test period. The body postures scored were slit stares, tail postures, scent marking of the cage/perches, piloerection, retreats, and arching of the back. Each animal was exposed to the threat stimulus twice on the test day before and after drug treatment. The difference between the two scores

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was analyzed using one-way analysis of variance followed by Dunnett's t-test. All drug treatments were carried out SC at least 2 hours after the first (control) threat. The pretreatment time for each compound was 40 minutes.

Rat Conflict Test

Rats were trained to press levers for food reward in operant chambers. The schedule consisted of alternations of four 4-minute unpunished periods on variable interval of 30 seconds signalled by chamber lights on and three 3-minute punished periods on fixed ratio 5 (by footshock concomitant to food delivery) signalled by chamber lights off. The degree of footshock was adjusted for each rat to obtain approximately 80% to 90% suppression of responding in comparison with unpunished responding. Rats received saline vehicle on training days.

RESULTS

The Mouse Light/Dark Box

The IP administration of gabapentin (3-100 mg/kg), 40 minutes before test, at doses of 10 and 30 mg/kg increased the time spent by mice in the illuminated side of the box, indicating an anxiolytic-like action (Figure 1). However, the effect disappeared at the highest dose of 100 mg/kg gabapentin (Figure 1).

The Rat Elevated X-Maze

The subcutaneous administration of gabapentin (3-100 mg/kg) increased the percent time spent (%TEOA) and percent entries (%EEOA) made onto the end half sections of the open arms (Figure 2). These increases indicate an anxiolytic-like action. Furthermore, an

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increase in total entries was also observed at 30 mg/kg.

The Marmoset Human Threat Test

5 The subcutaneous administration of gabapentin (10-300 mg/kg) decreased the number of postures emitted by marmosets in response to a human threat (Figure 3). This indicates an anxiolytic-like action. In this test, the activity of gabapentin was maintained over a
10 wide dose range.

Rat Conflict Test

 The administration of gabapentin 40 minutes before test dose-dependently (1-100 mg/kg) increased lever
15 pressing in the punished period with a minimum effective dose of 3 mg/kg producing a 65% increase. A maximal effect (179% increase) was observed with 30 mg/kg. At the highest dose tested (100 mg/kg), a reduction in lever pressing (37.4%) was noted in the
20 unpunished period, indicating sedation/ataxia, which may account for the apparent reduction in the effect observed in the punished phase. Similarly, chlordiazepoxide (1-100 mg/kg) dose-dependently increased lever pressing in the punished period with an
25 MED of 3 mg/kg producing a 128.4% increase. A maximal effect (330.0% increase) was observed with 30 mg/kg. Unpunished responding was not reduced at any of the doses tested (Figures 4a and 4b).

30 Further, it has been shown that the effects of gabapentin, i.e., anticonvulsant and anxiolytic activity, can be reversed by D-serine. This reversal of the activity of D-serine showed these properties share a common mechanism of action. It does not
35 involve a direct interaction between D-serine and gabapentin at the glycine/NMDA receptor complex as

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previous radioligand binding studies showed that gabapentin does not bind to the glycine/NMDA receptor (Suman-Chanhan, et al., Eur. J. Pharmacol.-Mol. Pharmacol. Sec., 244:293-301 (1993)).

5

BINDING OF GABAPENTIN TO THE $\alpha_2\delta$ SUBUNIT OF A
CALCIUM CHANNEL.

Summary

10 The partial N-terminal sequence of a pig brain
[³H]gabapentin binding protein has been determined.
The sequence of the first ten residues, EPFPSAVTIK is
identical to the N-terminal sequence of the mature $\alpha_2\delta$
subunit of the L-type Ca²⁺ channel from rabbit skeletal
15 muscle. The distribution of [³H]gabapentin binding
sites in rat tissues was broadly similar to that for
dihydropyridine-sensitive Ca²⁺ channels, as defined by
[³H]nitrendipine. The rank order of potency of ligands
acting at the muscle [³H]gabapentin binding site was
20 consistent with that reported previously for CNS sites.
[³H]Gabapentin is the first pharmacological agent
described that interacts with an $\alpha_2\delta$ subunit of a Ca²⁺
channel. This suggests that modulation of voltage-
dependent neuronal Ca²⁺ channels is important to the
25 antiepileptic action of gabapentin.

Materials

Pig brains were obtained from the local abattoir
and transported to the laboratory on ice. Buffer
30 components were obtained either from Sigma Chemical
Company, Poole, Dorset, UK or from FSA Supplies,
Loughborough, Leicestershire, UK. [³H]Gabapentin
(57.7 Ci/mmol) was custom synthesized by Amersham
International, Amersham, Bucks, UK. Unlabeled
35 gabapentin and the enantiomers of 3-isobutyl GABA were
obtained from Warner-Lambert, Ann Arbor, Michigan, USA.

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[³H]Nitrendipine (75.3 Ci/mmol) was obtained from DuPont (UK) Ltd, Stevenage, Herts, UK.

Methods

5 Binding of [³H]gabapentin to membranes was performed as described by Suman Chauhan, et al., Eur. J. Pharmacol, 244:293 (1993). [³H]Nitrendipine binding was carried out at room temperature for 30 minutes in 50 mM Tris/150 mM NaCl/2.5 mM CaCl₂ and reactions were terminated by rapid filtration through GF/B filters. Nonspecific binding was defined as that obtained in the presence of 1 μM nifedipine. Preparation of P₂ membrane fractions and purification of the [³H]gabapentin binding protein was as described 15 by Gee, et al., 1994, (submitted) except that the active fractions from Sephacryl S400 were further fractionated on a Cu²⁺-charged iminodiacetic acid-sepharose column. The final sample of purified protein (Approx. 5 μg) was electrophoresed in a 10% 20 polyacrylamide gel and transferred to an immobilon P membrane. The blot was stained with Coomassie Blue and the 130 kDa band excised and sequenced on an Applied Biosystems 477A Sequencer.

25 Results

Protein sequencing. An N-terminal sequence determination was made on each of two different preparations of the purified pig [³H]gabapentin binding protein. The sequence obtained for the first ten 30 cycles was EPFPSAVTIK. A search of the GenBank database revealed 100% homology with the first ten residues of the mature α₂δ subunit of the rabbit skeletal muscle L-type calcium channel (Ellis, et al., Science 241:1661 (1988)).

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Distribution of [³H]gabapentin binding sites in the rat. Radioligand binding assays using either [³H]gabapentin or [³H]nitrendipine were carried out using membranes prepared from a range of rat tissues. Relatively high levels of [³H]gabapentin binding sites were observed in skeletal muscle. Moderately high levels were found in cerebral cortex and cerebellum, with lower levels in forebrain and heart. Trace amounts of [³H]gabapentin binding sites were found in lung, spleen, liver, and kidney but pancreas and intestine were devoid of activity. The distribution of dihydropyridine-sensitive L-type Ca²⁺ calcium channels, as defined by [³H]nitrendipine, was broadly similar to that for [³H]gabapentin, although detailed differences in the relative amounts of radioligand binding in certain tissues were observed.

The partial N-terminal sequencing data indicates that the [³H]gabapentin binding protein from pig brain is an $\alpha_2\delta$ subunit of a voltage-dependent Ca²⁺ channel.

DESCRIPTION OF THE DRAWINGS

FIGURE 1. Effect of Gabapentin in the Mouse Light/Dark Box

Gabapentin was administered IP 40 minutes before the test. The time spent in the light side of the light/dark box was measured. Results are shown as the mean (vertical bars represent \pm SEM) of 10 animal per group.

*Significantly different from the vehicle (VEH) treated group, $p < 0.05$ (ANOVA followed by Dunnett's t-test).

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FIGURE 2. Effect of Gabapentin in the Rat Elevated X-Maze

5 Gabapentin was administered SC 40 minutes before test.
The percent time spent (%TOEA) and percent entries made
(%EEOA) on to the end half sections of the open arms,
and the total number of entries (TE) were measured.
Results are shown as the mean (vertical bars represent
10 \pm SEM) of 10 animals per group.
*Significantly different from vehicle-treated controls,
 $p < 0.05$ (ANOVA followed by Dunnett's t-test).

FIGURE 3. Effect of Gabapentin in the Marmoset Human Threat Test

15 Each animal was exposed to a 2-minute threat stimulus
before and after dosing. Test compounds were
administered SC 40 minutes before test. Results are
shown as percent decrease in postures (vertical bars
20 represent \pm SEM) in 5 to 6 animals per group.
*Significantly different from mean day controls,
 $p < 0.05$ (ANOVA followed by Dunnett's t-test).

FIGURE 4. Effect of Gabapentin and CDP in the Rat Conflict Test, and of Gabapentin in the Marmoset Human Threat Test

25 Gabapentin or chlordiazepoxide (CDP) were administered
40 minutes before test. The results are expressed as
mean percent increase or decrease of lever pressing
30 (vertical bars represent \pm SEM) of at least 5 animals
per group on test day compared with mean performances
obtained the 2 previous days following vehicle
administration. Significantly different from previous
35 control days
* $p < 0.05$, ** $p < 0.01$ (paired Student t-test).

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The results presented in the figures show that in addition to possessing anticonvulsant activity, gabapentin also shows potent anxiolytic-like action in animals. Thus, it showed good anxiolytic-like effects in the mouse light-dark box, the rat elevated X-maze, the rat conflict test, and the marmoset human threat test.

The dose range over which the anxiolytic-like effect of gabapentin was observed is similar to that producing anticonvulsant activity in animals. In the rat elevated X-maze and the marmoset human threat test, the magnitude of the effect was similar to that observed with benzodiazepine anxiolytics (Costall, et al., 1988; Singh, et al., 1991). The present data further shows that gabapentin produces a good anxiolytic-like effect in the rat conflict test. Most nonbenzodiazepine ligands that induce potent anxiolytic-like effects in the rat elevated X-maze and the marmoset human threat test show much weaker activity in shock-induced conflict tests. The ability of gabapentin to induce a good disinhibition of conflict behavior may represent an advantage over compounds such as buspirone and those currently undergoing clinical investigation for treatment of anxiety but are weakly active in this test (e.g., CCK₈ and 5-HT₃ receptor antagonists; see Broekkamp, et al., 1989 for review; Singh, et al., 1991).

The results from the human threat test particularly suggest a role for gabapentin in the treatment of panic.

Examples of formulations of the subject compounds or salts thereof are illustrated by the following examples.

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EXAMPLE 1

Injectables

1 mg to 100 mg/mL

Gabapentin

5 Water for Injection USP q.s.

The compound or a suitable salt thereof is dissolved in water and passed through a 0.2-micron filter. Aliquots of the filtered solution are added to ampoules or vials, sealed and sterilized.

10

EXAMPLE 2

Capsules

50 mg, 100 mg, 200 mg, 300 mg or 400 mg

Gabapentin, 250 g

15 Lactose USP, Anhydrous q.s. or 250 g

Sterotex Powder HM, 5 g

Combine the compound and the lactose in a tumble blend for 2 minutes, blend for 1 minute with the intensifier bar, and then tumble blend again for 1 minute. A portion of the blend is then mixed with the Sterotex powder, passed through a #30 screen and added back to the remainder of the blend. The mixed ingredients are then blended for 1 minute, blended with the intensifier bar for 30 seconds, and tumble blended for an additional minute. The appropriately sized capsules are filled with 141 mg, 352.5 mg, or 705 mg of the blend, respectively, for the 50 mg, 125 mg, and 250 mg containing capsules.

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EXAMPLE 3

Tablets

5 mg, 100 mg, 200 mg, 300 mg,
400 mg, 500 mg or 600 mg

5 Gabapentin, 125 g
Corn Starch NF, 200 g
Cellulose, Microcrystalline, 46 g
Sterotex Powder HM, 4 g
Purified Water q.s. or 300 mL

10 Combine the corn starch, the cellulose, and the
compound together in a planetary mixer and mix for
2 minutes. Add the water to this combination and mix
for 1 minute. The resulting mix is spread on trays and
dried in a hot air oven at 50°C until a moisture level
15 of 1 to 2 percent is obtained. The dried mix is then
milled with a Fitzmill through a #RH2B screen, and
added back to the milled mixture and the total blended
for 5 minutes by drum rolling. Compressed tablets of
150 mg, 375 mg, and 750 mg, respectively, of the total
20 mix are formed with appropriate sized punches the
50 mg, 125 mg, or 50 mg containing tablets.

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CLAIMS

1. A method for treating anxiety which comprises administering a therapeutically effective amount of a compound of formula



10 wherein R_1 is hydrogen or a lower alkyl and n is 4, 5, or 6 or a pharmaceutically acceptable salt thereof, in unit dosage form, to a mammal in need of said treatment.

2. A method of treating and/or preventing panic which comprises administering a therapeutically effective amount of a compound of formula



10 wherein R_1 is hydrogen or a lower alkyl and n is 4, 5, or 6 or a pharmaceutically acceptable salt thereof, in unit dosage form, to a mammal in need of said treatment.

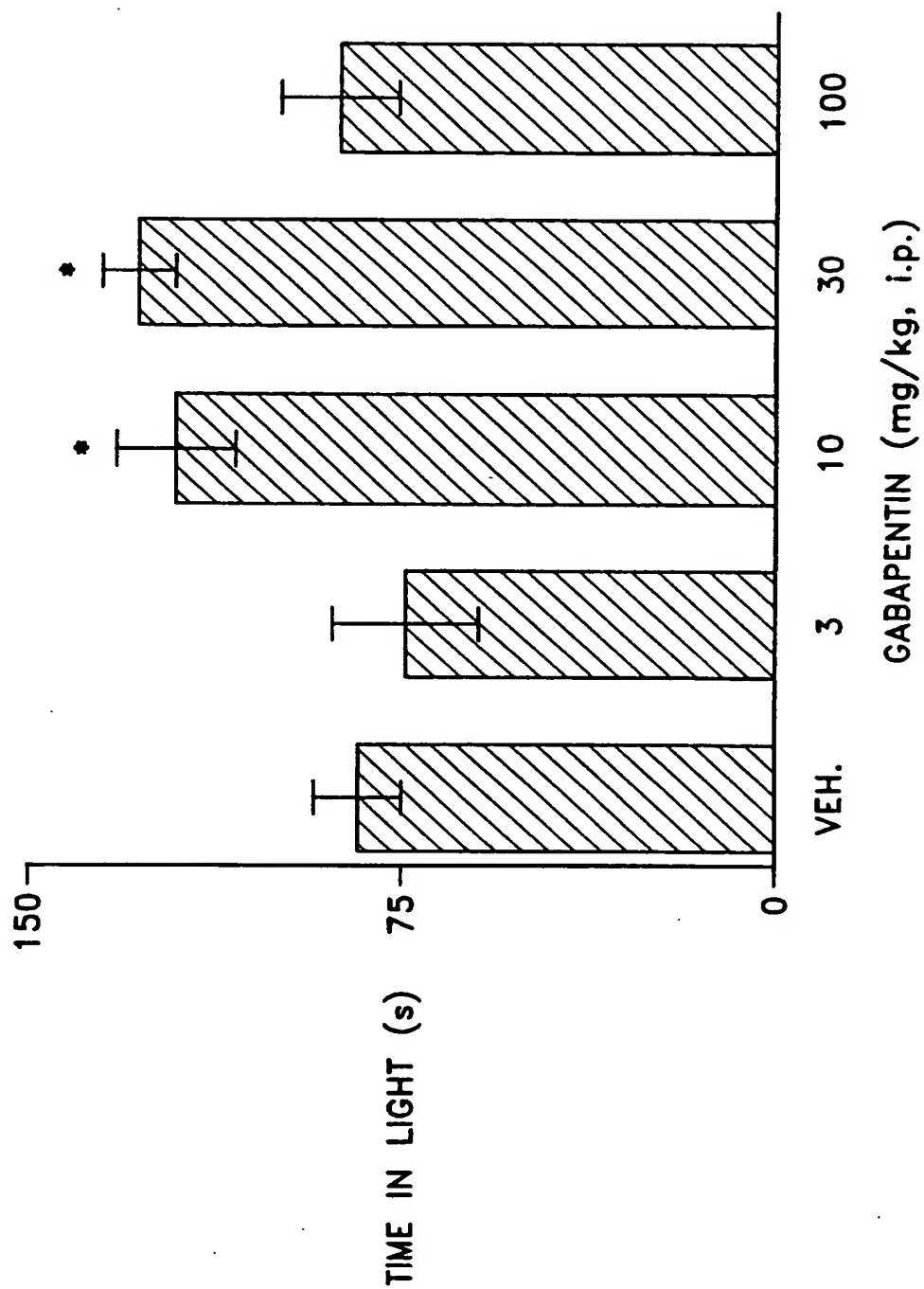
3. A method according to Claim 1 or Claim 2 wherein the compound is gabapentin or a pharmaceutically acceptable salt thereof.

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4. A method according to Claim 1 or Claim 2 wherein an individual dose is 5 mg to 50 mg parenterally or 50 to 600 mg enterally of the compound or a pharmaceutically acceptable salt thereof is administered.
- 5
5. The purified gabapentin binding protein having a sequence of the first ten amino acid residues of ZPFPSAVTIK and being an $\alpha_2\delta$ subunit.
6. Pharmacological agents binding to the [^3H] gabapentin binding protein.
7. Pharmacological agents interacting with an $\alpha_2\delta$ subunit of a Ca^{2+} channel.

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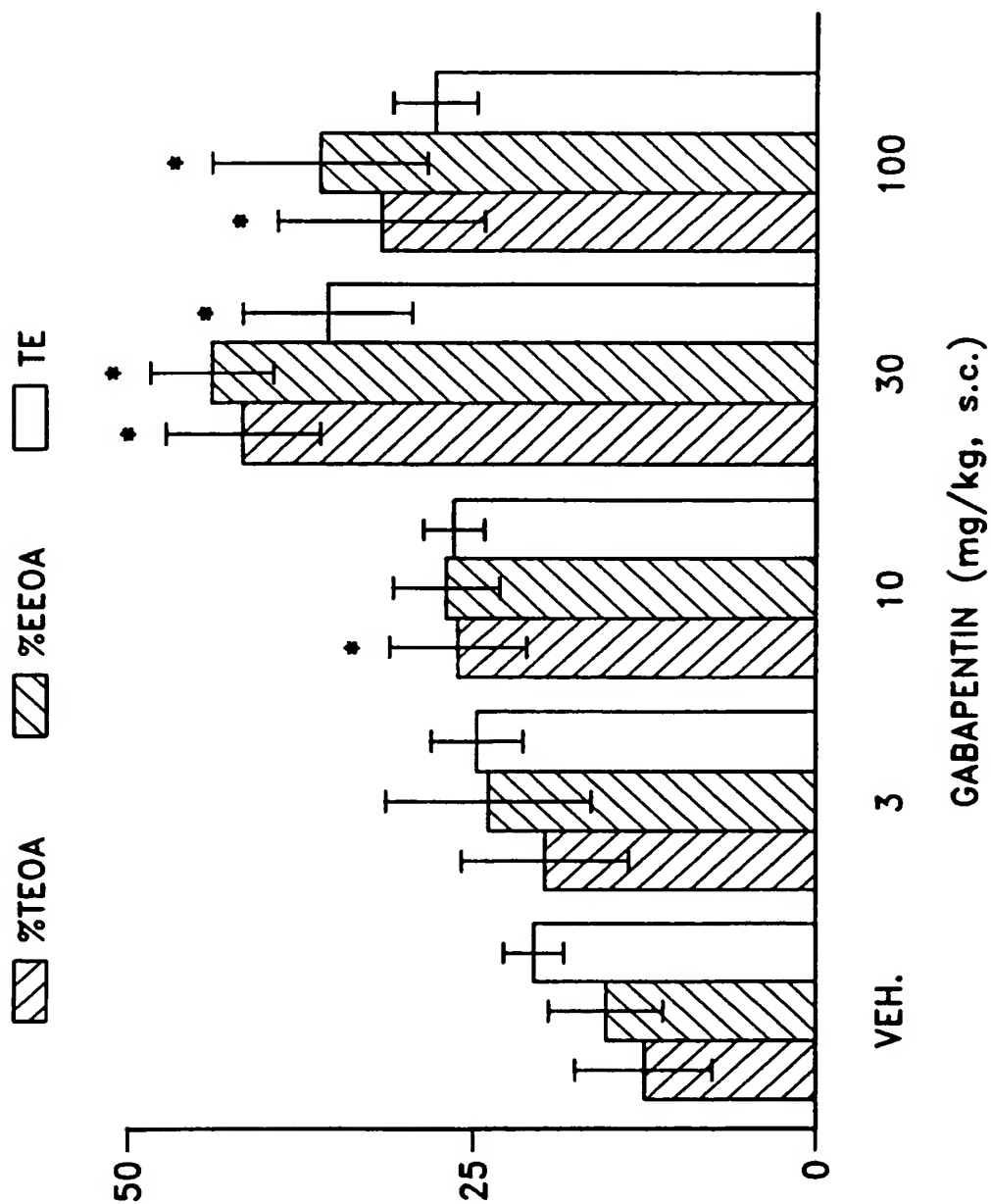
FIG-1



SUBSTITUTE SHEET (RULE 26)

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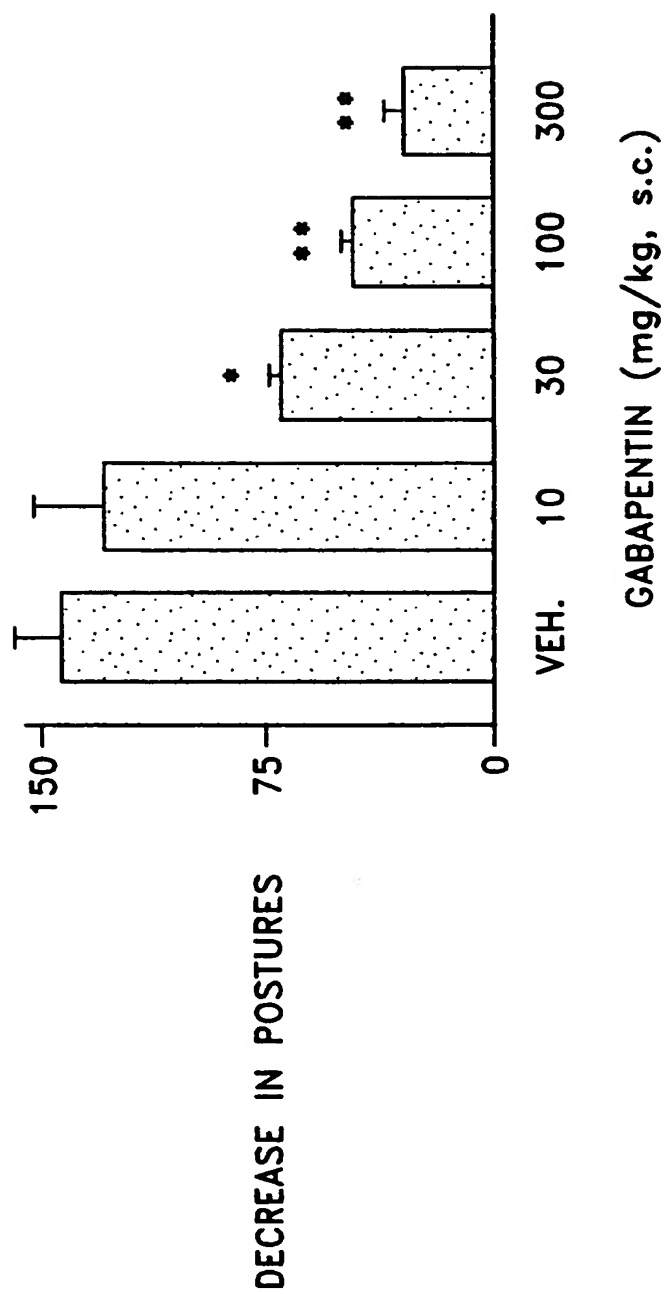
FIG-2



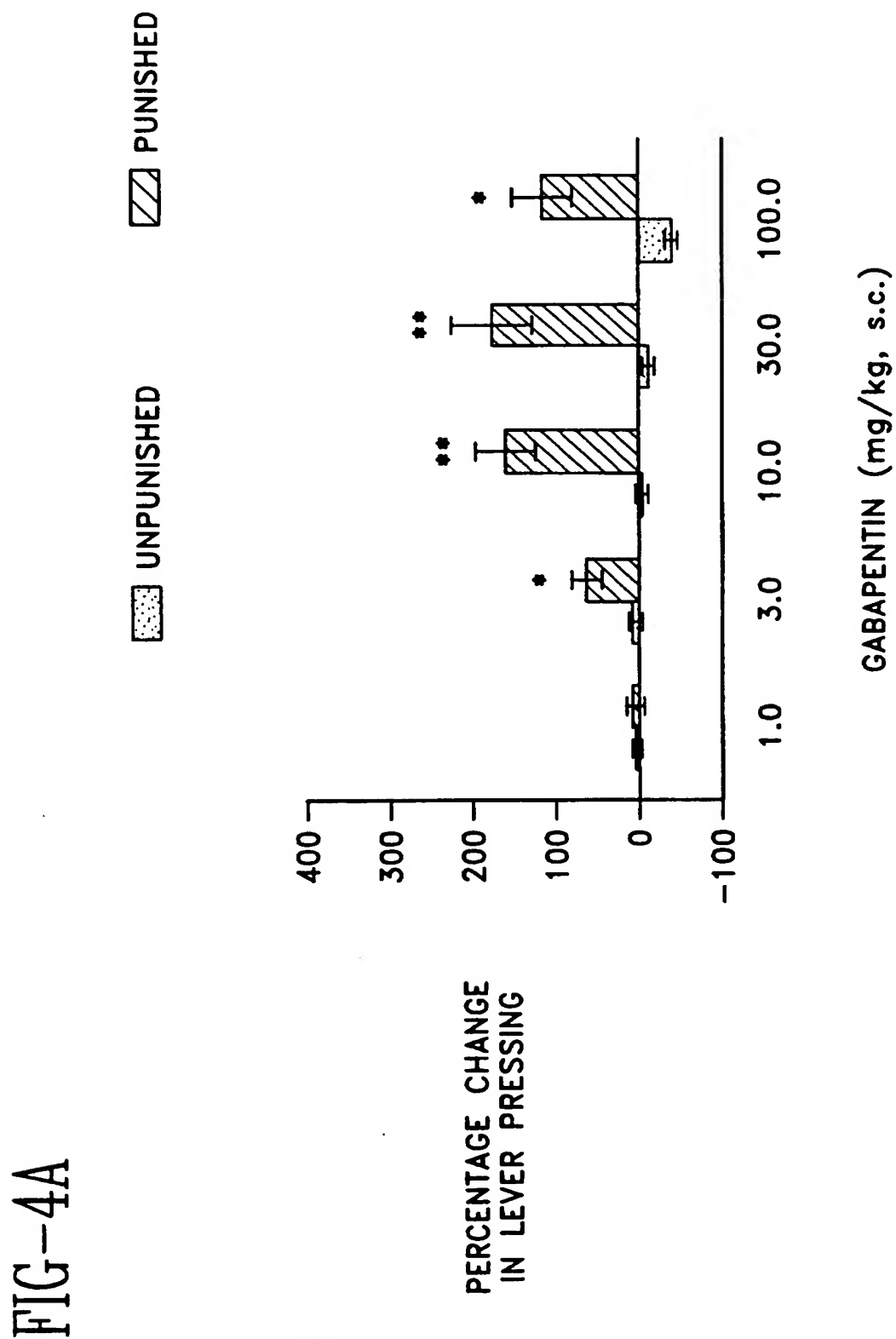
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FIG-3



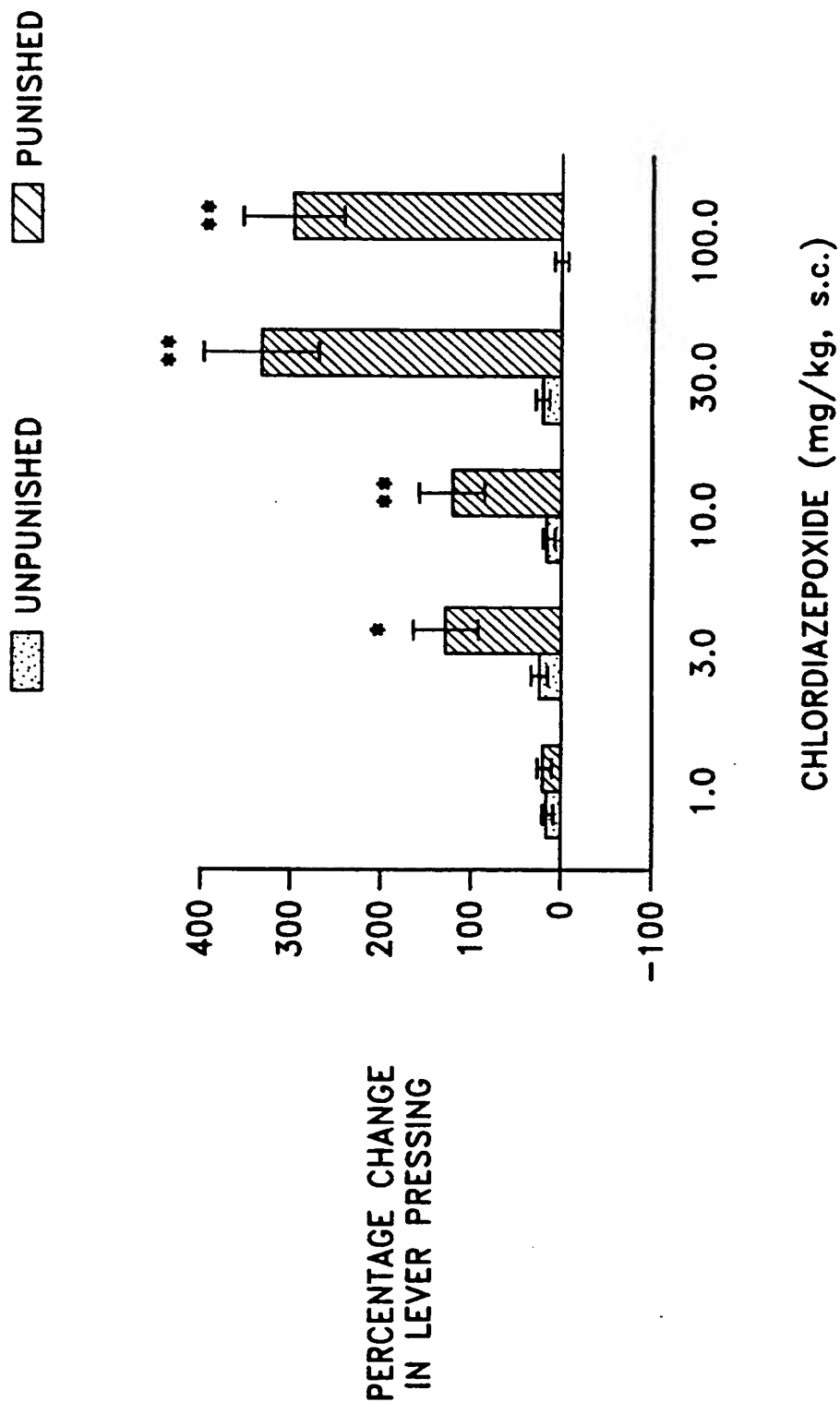
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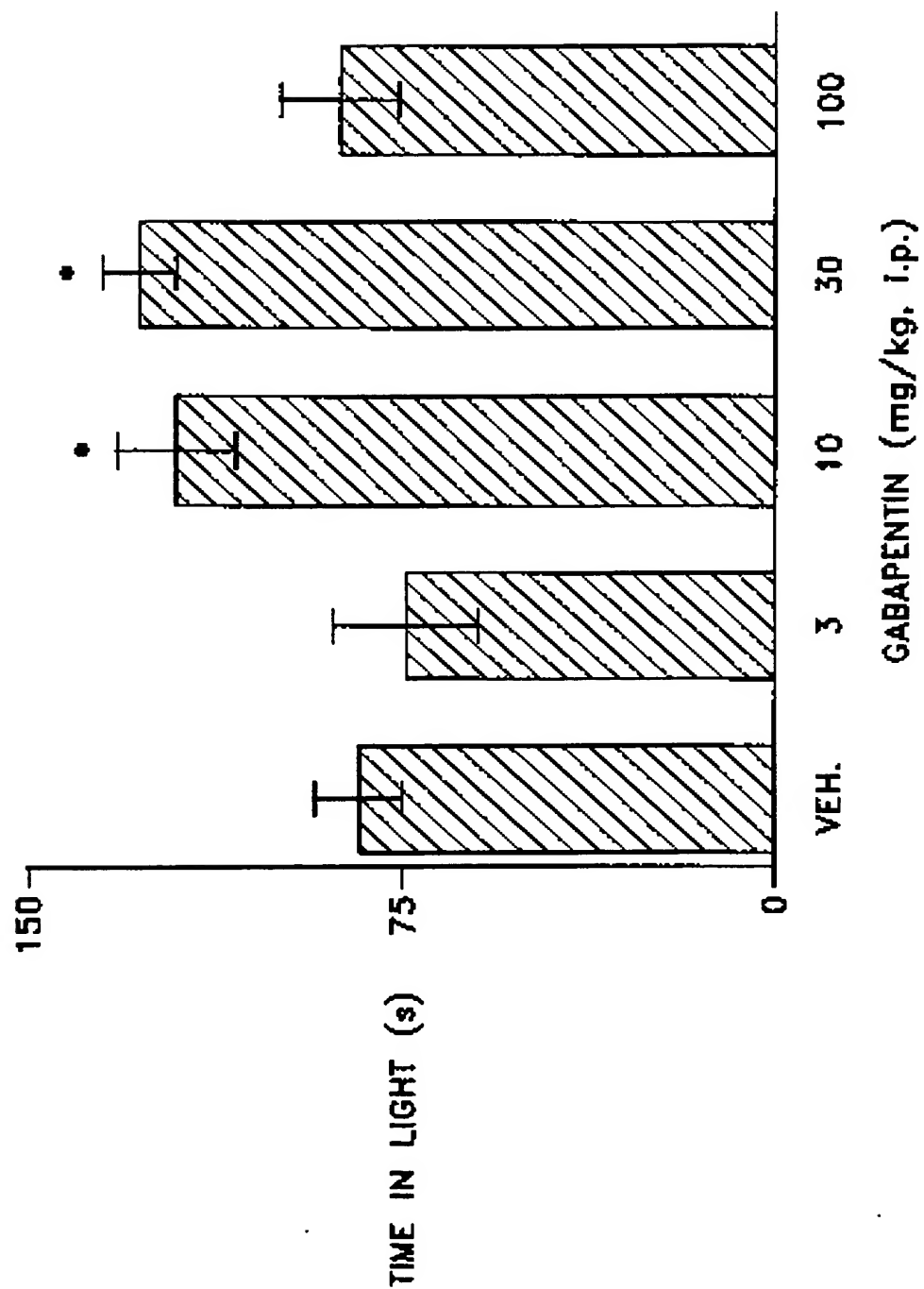
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FIG-4B



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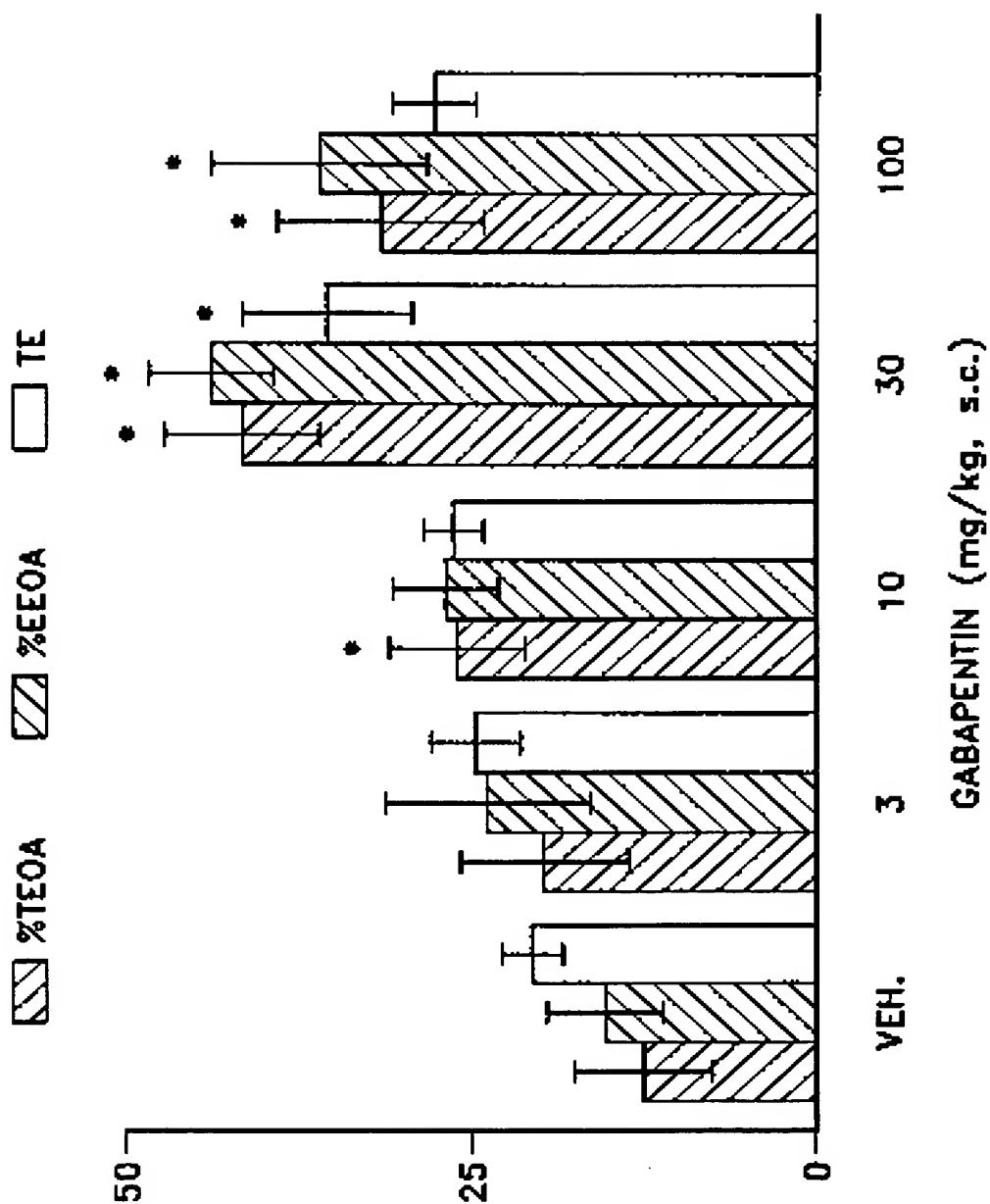
FIG-1



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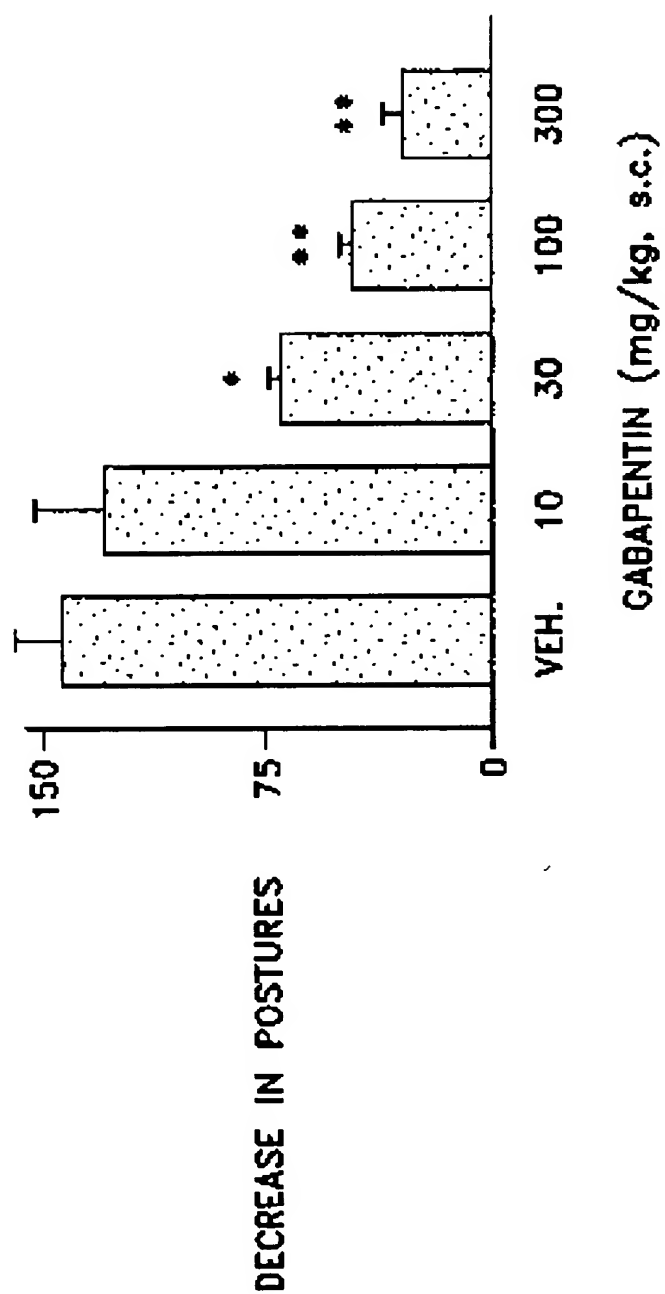
FIG-2



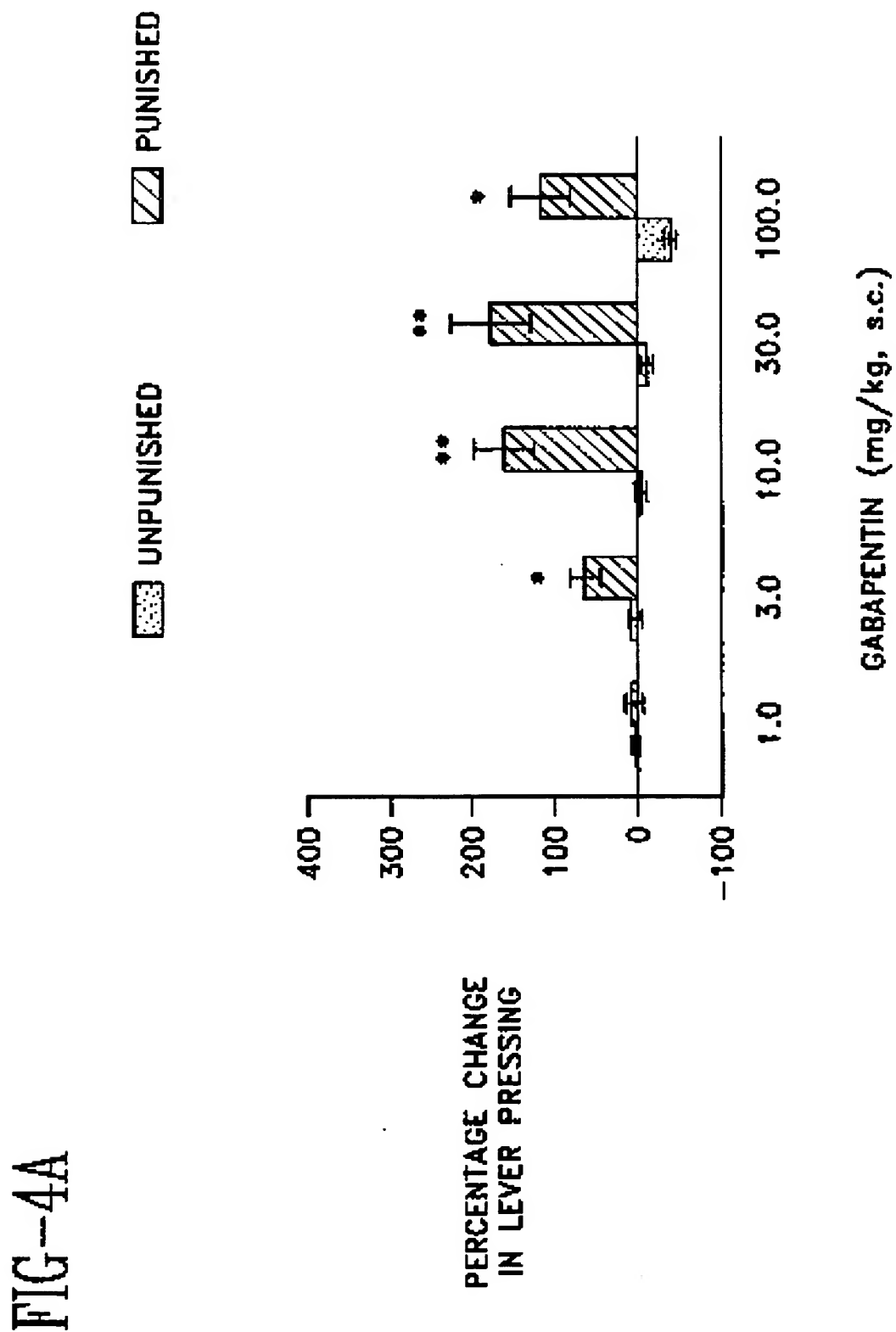
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FIG-3



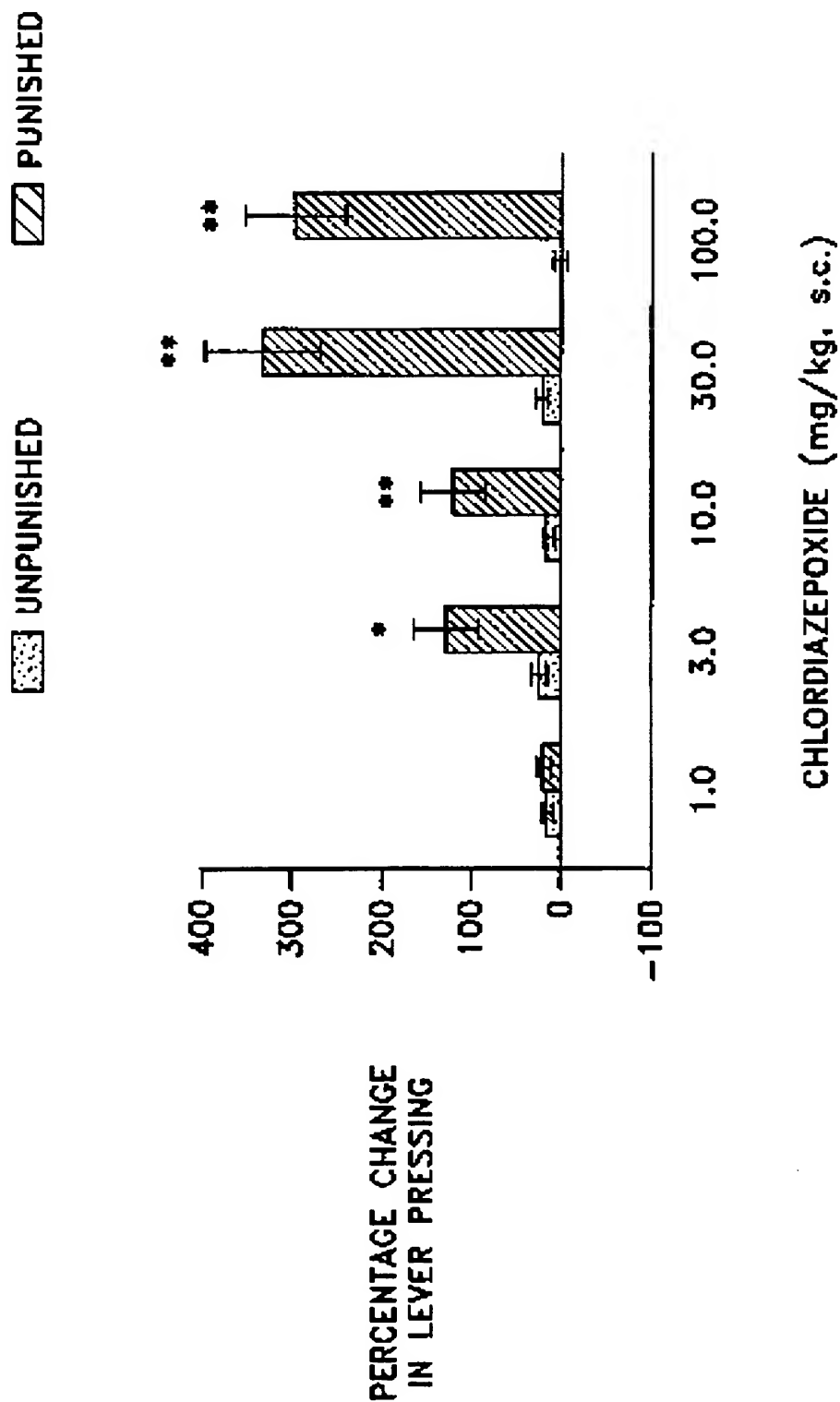
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FIG-4B



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/195, 31/22, 31/00, C07K 14/47		A3	(11) International Publication Number: WO 96/03122
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(21) International Application Number: PCT/US95/08702		(81) Designated States: AU, CA, CZ, EE, HU, JP, LT, LV, MX, NZ, PL, RO, RU, SI, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 11 July 1995 (11.07.95)			
(30) Priority Data: 08/281,285 27 July 1994 (27.07.94) US 08/445,398 6 June 1995 (06.06.95) US		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).		(88) Date of publication of the international search report: 18 July 1996 (18.07.96)	
(72) Inventors: WOODRUFF, Geoffrey, Neil; Turks House, Dassels, Braughing, Nr. Ware, Herts SG9 2NN (GB). GEE, Nicolas, S.; 30 Rainsford Road, Stansted, Essex CM24 8DU (GB). SINGH, Lakhbir, 23 Hinton View, Haddenham, Cambridgeshire CB6 5SP (GB). BROWN, Jason, P.; 9 Church Street, Stapleford, Cambridge CB2 5DS (GB).			
(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.			

(54) Title: USE OF GABAPENTIN IN THE TREATMENT OF ANXIETY AND PANIC

(57) Abstract

The instant invention is novel uses of known cyclic amino acids. Such compounds as gabapentin are useful in the treatment of anxiety and in the treatment and/or prevention of panic attacks. The partial N-terminal sequence of the gabapentin binding protein has been determined to be identical to the N-terminal sequence of the mature $\alpha_2\delta$ subunit of the L-type Ca^{2+} channel from rabbit skeletal muscle.

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INTERNATIONAL SEARCH REPORT

International Application No
/US 95/08702

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/195 A61K31/22 A61K31/00 C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EPILEPSIA, vol. 34, no. sup.6, 1993 page 45 LEIDERMAN ET AL 'Gabapentin therapy and quality of life: side effects in placebo-controlled studies' * right hand col. *	1-4
A	DRUG EVALUATION, vol. 46, no. 3, 1993 pages 409-27, GOA ET AL 'Gabapentin' cited in the application see the whole document	1-4
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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A document member of the same patent family

Date of the actual completion of the international search

23 April 1996

Date of mailing of the international search report

21.05.96

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 22302 (FRACTAL LAB. INC.) 23 December 1992 * p.9, 1.16-20 *	1
Y	* p.9, 1.16-20 *	2-4,7
X	--- SCIENCE, vol. 241, 1988 pages 1661-4, ELLIS ET AL 'Sequence and expression of mRNAs encoding the alpha1 and alpha2 subunits of a DHP-sensitive calcium channel' cited in the application * abstract; p.1661, Fig. 1 *	5
Y	see the whole document	6,7
X	--- EUROPEAN J. OF PHARMACOLOGY, MOLECULAR PHARMACOLOGY SECTION, vol. 244, 1993 pages 303-9, HILL ET AL 'Localization of [3H]gabapentin to a novel site in rat brain: autoradiographic studies' cited in the application * Abstract; p.308-9, Note added in proof *	6,7
Y	see the whole document	5
X	--- EUROPEAN J. OF PHARMACOLOGY, MOLECULAR PHARMACOLOGY SECTION, vol. 244, 1993 pages 293-01, SUMAN-CHAUHAN ET AL 'Characterization of [3H]gabapentin binding to a novel site in rat brain: homogenate binding studies' cited in the application * abstract; Tables 1-5; p.300, 3rd full par.; p.301, note added in proof *	6,7
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X	--- EUROPEAN J. OF PHARMACOLOGY, MOLECULAR PHARMACOLOGY SECTION, vol. 247, 1993 pages 341-5, THURLOW ET AL '[3H]Gabapentin may label a system-L-like neutral amino acid carrier in brain' * Abstract; Table 1; p.343-4, Discussion *	6,7
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INTERNATIONAL SEARCH REPORT

International Application No
/US 95/08702

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 9, 4 March 1994 pages 6716-24, DE WAARD ET AL 'Functional properties of the purified N-type Ca++ Channel from rabbit brain' * Abstract; p.6719-23, Discussion; Table 2 *	7
Y	* p.6716, left hand col., 1.1-right hand col., 1.18 *	5,6
Y	--- THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 25, 1990 pages 14738-41, DE JONGH ET AL 'Subunits of purified calcium channels' see the whole document	5,7
X	--- BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 4, no. 6, 1994 pages 823-6, YUEN ET AL 'Enantioselective synthesis of PD144723: a potent stereospecific anticonvulsant' see the whole document	6,7
X	--- WO,A,93 23383 (NORTHWESTERN UNIVERSITY) 25 November 1993 cited in the application * claims; table 6 *	6,7
Y	see the whole document	1-4
X	--- EUROPEAN J. OF PHARMACOLOGY, MOLECULAR PHARMACOLOGY SECTION, vol. 227, 1992 pages 363-70, TOKUMARU ET AL 'Purification of the cardiac 1,4-dihydropyridine receptor using immunoaffinity chromatography with a monoclonal antibody against the alpha2delta subunit of the skeletal muscle dihydropyridine receptor' *Abstract ; p.363, left col. 1.1-right col.2, 1.12; *	7
Y	*abstract; p.368-9, Discussion; Fig 5 *	5
	--- -/--	

INTERNATIONAL SEARCH REPORT

Inter. nat. Application No
PCT/US 95/08702

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PROC. NATL. ACAD. SCI. USA, vol. 86, 1989 pages 8585-9, DE JONGH ET AL 'Subunits of purified calcium channels: a 212-kDa form of alpha1 and partial amino acid sequence of a phosphorylation site of an independent beta subunit' see the whole document ---	5,7
X	EP,A,0 400 665 (SQUIBB & SONS INC.) 5 December 1990 * p.1, 1.1-37 *	7
Y	see page 1-4 -----	1-4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/08702

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. CLAIMS 1-4
2. CLAIM 5
3. CLAIM 6
4. CLAIM 7

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

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sheet C

The present application does not meet the requirement of R.13.1 PCT as the present application lacks unity, both a priori and a posteriori.

Gabapentin and derivatives thereof are already known for therapeutic purposes. Therefore, the present inventive concept is based on the therapeutic indication of gabapentin and derivatives thereof presently claimed, that is, the antianxiety effect.

The present application lacks unity a priori. There is no inventive concept or link between on the one hand claims 1-4 and on the other hand the binding protein of claim 5 or the pharmacological agents of claims 6 or 7. For instance, the pharmacological agents binding on the $\alpha 2\delta$ subunit of the calcium channel does not necessarily act as anxiolytic.

In addition, the anxiolytic effect of gabapentin is already known from *Epilepsia* (1993), vol.34, Suppl. 6, p.45, so that, claims 1-4 lacks novelty.

Accordingly, the IPEA considers that the present application comprises 4 different "inventions" which are separately indicated in present sheet B.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
US 95/08702

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9222302	23-12-92	US-A- 5189026 AU-B- 2160492 US-A- 5302583	23-02-93 12-01-93 12-04-94
WO-A-9323383	25-11-93	AU-B- 4379493 CA-A- 2134674 CZ-A- 9402849 EP-A- 0641330 FI-A- 945426 HU-A- 71522 JP-T- 7508288 NO-A- 944370 SK-A- 139594	13-12-93 25-11-93 15-03-95 08-03-95 18-11-94 28-12-95 14-09-95 21-11-94 10-05-95
EP-A-400665	05-12-90	AU-B- 633565 AU-B- 5494890 CA-A- 2016465 JP-A- 3034926 US-A- 5089502	04-02-93 06-12-90 02-12-90 14-02-91 18-02-92

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